# EARLY MYOCARDIAL INJURY IN CHILDREN ON CANCER CHEMOTHERAPY

**A Research Project in Partial Fulfilment for the Degree of Masters of Medicine (Paediatrics and Child Health), University of Nairobi**

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## DECLARATION

This dissertation is my original work and has not, to my knowledge, been published or presented for any degree in any other university or forum.

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# LIST OF ABBREVIATIONS

**ALL**-Acute lymphocytic leukaemia

**AML**- Acute myeloid leukaemia

**CHD**- Congenital heart disease

**CI**- Confidence interval.

**CTnI**- Cardiac troponin I

**CTnT**- Cardiac troponin T

**ECG**- Electrocardiogram.

**ECHO**- Echocardiography

**EF**- Ejection Fraction.

**FS**- Fractional shortening

**KNH**- Kenyatta National Hospital.

**LV**- Left ventricular

**LVEDD**-Left ventricular end diastolic dimensions

**LVESD**-Left ventricular end systolic dimensions

**LVEF**- Left ventricular Ejection fraction

**NHL**-Non-Hodgkin's Lymphoma

**NPV**- Negative predictive value

**OR**- Odds Ratio

**PPV**- Positive predictive value

**RCT**- Randomised Control trial

**RHD**- Rheumatic heart disease

# STUDY DEFINITIONS

1. Cardiotoxicity is defined as abnormal cardiac functioning that commonly occurs secondary to use of anticancer drugs, as manifested by:

- An elevated cardiac troponin T (greater than 0.014 ng/ml).
- Fractional shortening of less than 29% on Echocardiography.

2. Myocardial Injury is defined as inflammation of the myocardium as detected by an elevated cardiac troponin T or abnormal echocardiographic findings, as stated above.

3. Early myocardial injury is defined as myocardial injury occurring during treatment and within the $1^{st}$ year of completion of treatment with anti-cancer agents.

4. Late myocardial injury is defined as myocardial injury occurring after 1 year of completion of treatment with anti-cancer agents.

## ABSTRACT

**BACKGROUND:** Use of chemotherapeutic agents has been associated with cardiac toxicities. Detection of early cardiac toxicities of cancer chemotherapy is essential so as to prevent occurrence of late cardiac toxicities. Cardiac troponins have been shown to detect subclinical injury much earlier than echocardiography.

**OBJECTIVE:** To determine the prevalence and associated factors of myocardial injury as determined by elevated cardiac troponin T (cTnT), in children on cancer chemotherapy at Kenyatta National hospital(KNH).

**METHODOLOGY:** A hospital based cross-sectional study in children aged 1 month to 18 years who had a diagnosis of cancer and were admitted to KNH. The patients underwent Echocardiography (ECHO) before their scheduled chemotherapy infusion. Twenty four (24) hours after the chemotherapy infusion the patients had an evaluation of the serum cardiac troponin T (CTnT) and a repeat echocardiography (ECHO). Myocardial injury was defined as cTnT level greater than 0.014 ng/ml or a Fractional shortening of <29% respectively on ECHO.

**STUDY RESULTS:** One hundred (100) children were included in the final analysis. Thirty-two percent (32%) of the study population had an elevated cTnT. A cumulative Adriamycin dose of >175mg/m$^2$ was significantly associated with and elevated cTnT OR 10.76 (95% CI 1.18-97.92) p=0.035. Diagnosis of Nephroblastoma was also significantly associated with an elevated cTnT OR 3 (95% CI 1.23-7.26) p=0.015. Nine percent (9%) of the participants had echocardiographic evidence of myocardial injury. There was no association between elevated cTnT and a reduced fractional shortening.

**CONCLUSION:** Thirty two percent of the study population had myocardial injury as determined by an elevated cTnT and 9% had echocardiographic evidence of myocardial injury.

**RECOMMENDATION:** CTnT should be considered as a screening test for myocardial injury in children on cancer chemotherapy.

# CHAPTER ONE

## INTRODUCTION AND LITERATURE REVIEW

### 1.1 Background

Cancer is defined as the uncontrolled proliferation of abnormal cells. These abnormal cells can in turn seed into distant organs, a process known as metastasis. The annual frequency of childhood cancers in Kenyatta National hospital is estimated to be 125 cases per year. A review of childhood cancers at KNH by Macharia in 1996 (1), found a hospital based prevalence of 1.27%. Another review of childhood cancers in Kenya by Mwanda in 1997(2), which included 7 provincial hospitals and KNH, found 157 cases. The most common childhood cancers were: Burkitt's lymphoma 45%, Nephroblastoma 14%, Hodgkin's lymphoma 9.5%, acute lymphocytic leukaemia 7.6%, Retinoblastoma 5.7%, and acute myeloid leukaemia 5.1%. This study showed that the commonest childhood tumour in Kenya was Burkitt's lymphoma and the commonest solid tumour in children was Nephroblastoma.

Management of paediatric malignancies involves a multimodal approach which includes use of Chemotherapy, radiotherapy and surgery. The mainstay of management of most malignancies however, is chemotherapy. Chemotherapy has significantly increased the survival of most children with malignancies. The use of some of these chemotherapeutic agents is limited by their toxicity profiles especially cardiac toxicity. Some of these drugs have been known to cause dilated cardiomyopathy, congestive cardiac failure and even sudden cardiac death. It is thus essential to detect early cardiac toxicities of cancer chemotherapy so as to prevent occurrence of late cardiac toxicities. Echocardiography, which is the current standard of care, reliably detects late cardiac changes of chemotherapy induced cardiac injury. Cardiac troponins are the best known molecular markers of myocardial injury. They have been shown to reliably detect early myocardial injury. They also have a high positive and negative predictive value in detection of chemotherapy induced cardiac injury.

**1.2 Chemotherapy Induced Cardio-Toxicity**

There are several chemotherapeutic agents that have been associated with cardiotoxicity. These include: Anthracyclines agents, Alkylating agents, Taxanes and Monoclonal antibodies such as transtuzumab.

Commonly, 2 forms of chemotherapy-induced cardiotoxicity may be distinguished (3):

- Type 1 cardiotoxicity- This is irreversible toxicity that is usually dose dependent. The prototype drugs that cause this type of cardiotoxicity are the anthracyclines (mainly doxorubicin) and alkylating agents (mainly cyclophosphamide).
- Type 2 cardiotoxicity-This is a reversible cardiotoxicity that is not dose dependent. The prototype drug causing this type of cardiotoxicity is the monoclonal antibody group of drugs.

The irreversible type of cardiotoxicity (type 1) which has been best studied and established in patients who have received anthracyclines is further divided into 2 main types, namely (4):

Acute or subacute cardiotoxicity, can occur anytime from the initiation of chemotherapy up to 2 weeks after termination of treatment. The clinical presentation usually ranges from ventricular arrhythmias, prolonged QT intervals, to acute coronary syndromes and even acute heart failure. Chronic cardiotoxicity, may be differentiated in 2 subtypes based on the timing of onset of clinical symptoms: Early onset chronic progressive cardiotoxicity-Occurs within the first year after completion of treatment. Late onset chronic progressive-Occurs after 1 year of completion of treatment to 10years or more after completion of treatment. Typical signs of chronic cardiotoxicity include asymptomatic diastolic and/or systolic left ventricular dysfunction that leads to dilated cardiomyopathy with congestive heart failure and death. This occurs more than one year after completion of treatment.

**1.3 Pathophysiology of Cardiotoxicity**

Given that the cardiotoxic effects of anthracyclines have been well studied, an outline of the mechanisms of cardiotoxicity of anthracyclines is shown in figure 1.0 below:
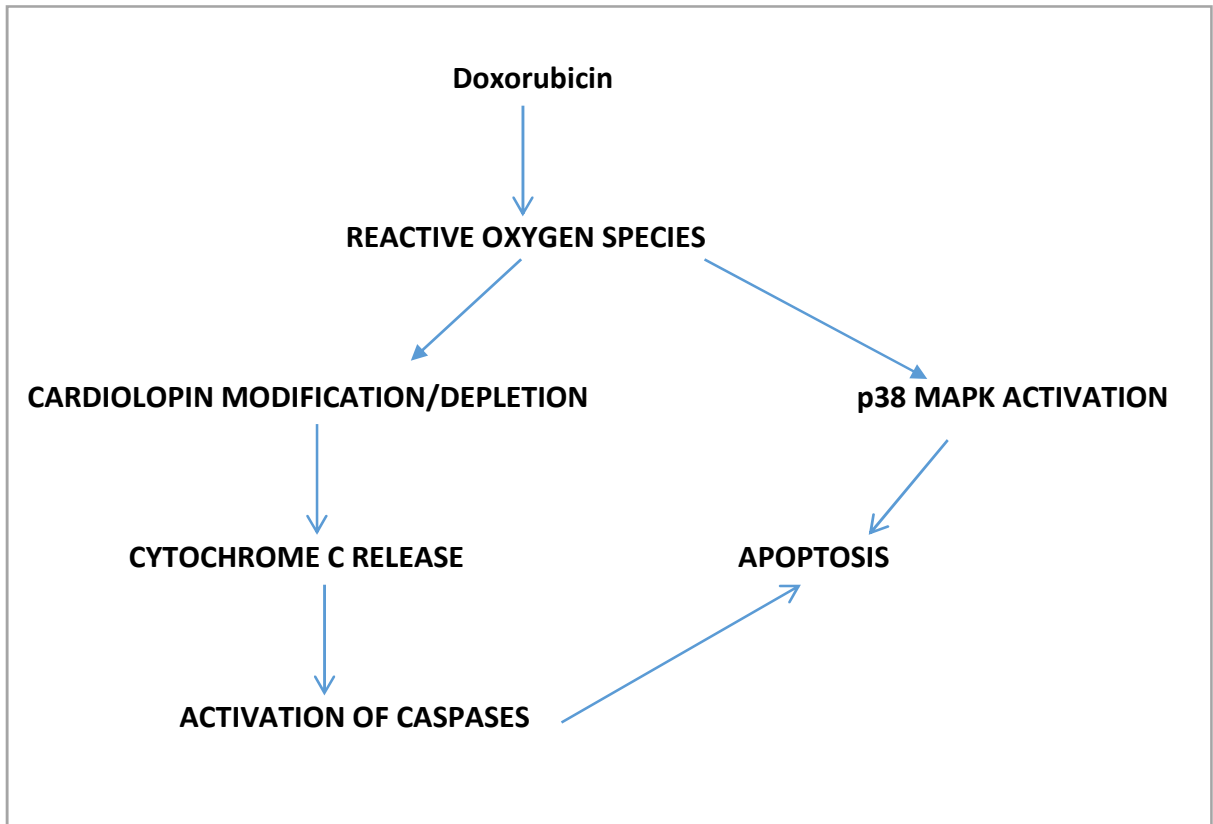
**Figure 1.0: Pathogenesis of Adriamycin induced myocardial injury**

The toxicity of doxorubicin is mainly due to free radical formation caused by doxorubicin metabolism. Doxorubicin is reduced by NADH dehydrogenase in mitochondria, to form a semi Quinone radical that reacts with molecular oxygen to form the superoxide radical and other free radicals such as hydrogen peroxide and hydroxyl ions (5).

Doxorubicin-iron complexes have also been shown to catalyse a Fenton reaction resulting in conversion of hydrogen peroxide to a hydroxyl radical. These free oxidative radicals cause cell death via apoptotic pathways mainly by activation of caspase 3 and caspase 9.This results in myofibrillar damage and leakage of cardiac troponins into the systemic circulation and the resulting systolic ventricular dysfunction.

**1.4 Epidemiology of Chemotherapy Induced Cardiotoxicity**

Globally, the prevalence of cardiotoxicity in childhood survivors is as high as 65%. This is based on a study by Lipshultz et el in 1991 (6),where 115 children, who had been managed for Acute lymphocytic leukaemia (ALL) with anthracycline containing regimens, were followed up for a median time of 6 years. Sixty five percent (65%) of these children had detectable echocardiographic abnormalities at the time of follow up. The major abnormalities detected via echocardiography included reduction of the left ventricular ejection fraction to less than 55% and thinning of the posterior left ventricular walls. 10% of these children developed symptomatic heart failure and 2% of the study population underwent cardiac transplantation due to dilated cardiomyopathy.

According to the childhood cancer survivor study, which had a cohort of 20,483 cases, childhood cancer survivors do have an 8.4 fold increase in mortality, 5 years after diagnosis compared to the general population (7). One of the factors that was associated with this increased likelihood of mortality was cardiovascular morbidity. Other factors that contributed to this increased mortality included tumour recurrence, development of secondary neoplasms and pulmonary pathologies.

In Kenya, Kariuki et al (8) did demonstrate that up to 16% of children with cancer had evidence of cardiac dysfunction, when compared to normal controls. This study evaluated children before and during treatment and compared them to normal controls who did not have cancer. The abnormal cardiac status in children with malignancies was attributable to the malignancies themselves. Another Kenyan study by Shiroya et al in 2006 (9), showed that up to 29% (32/111) of children on cancer chemotherapy in KNH had abnormal cardiac function as determined by echocardiography. This study also demonstrated that a cumulative dose of doxorubicin of >200mg/m2 was associated with a 4.4 fold increased risk of developing cardiac dysfunction.

**1.5 Risk Factors of Cardiotoxicity in Children with Cancer**

There are several risk factors that are known to increase the risk of cardiac dysfunction in children with cancers.

**1.5.1 Cumulative Anthracycline Dose**

Although doxorubicin has become one of the most effective chemotherapeutic agents, it was noted early on that its use was complicated by the development of heart failure. In a retrospective analysis of over 4000 patients receiving doxorubicin performed by Von Hoff and colleagues, 2.2% of the patients developed clinical signs and symptoms of congestive heart failure.(10) This study was based on clinical features of heart failure thus the authors acknowledged that rates of subclinical left ventricular dysfunction could have been higher.

**Table 1.1: cumulative anthracycline dose and relative risk of cardiac toxicity (5)**

| Cumulative dose (mg/m$^2$) | Patients with CHF (%) |
|---|---|
| 150 | 0.2 |
| 300 | 1.6 |
| 450 | 3.3 |
| 600 | 8.7 |

In African children, cardiac toxicity occurs even at much lower cumulative anthracycline doses. Shiroya et al demonstrated that at anthracycline doses of >200mg/m2, there was a 4.4 fold increased risk of developing cardiac toxicity, as shown in the table 1.2 below (9).

**Table 1.2: Cumulative anthracycline dose and risk of cardiac dysfunction in Kenyan children (9)**

| CUMULATIVE ANTHRACY-CLINE DOSE (mg/m$^2$) | ODD RATIO (95% CI) | P-VALUE |
|---|---|---|
| <30 | 1 | - |
| 30.1-94 | 2.5 (0.7-8.9) | 0.2 |
| 94.1-201 | 1.2 (0.3-4.5) | 1.0 |
| >201 | 4.4 (1.3-15.4) | 0.02 |

In the childhood cancer survivor study cohort of 20,483 survivors of childhood malignancies, use of <250 mg/m2 cumulative anthracycline dose was associated with a 2.4 fold increased risk of congestive heart failure compared to those who did not receive anthracyclines (7). This risk increased to 5.2 with use of > 250mg/m2 of anthracyclines. Lipshultz et al also demonstrated that at cumulative doses of >228mg/m2, 65 %( 72/112) children had echocardiographic evidence of cardiac toxicity. (6)

### 1.5.2 Female Gender

Gender had been evaluated as a risk factor for cardiac dysfunction in children with cancer. Female patients have a twofold increased risk of developing cardiac dysfunction compared to male patients. In a retrospective analysis of 115 children who had been treated for ALL and osteogenic sarcoma with anthracycline containing regimens, Lipshultz et al demonstrated that 45% of females had depressed left ventricular function compared to only 12% of male patients. (11) They also found that this reduced left ventricular function was more pronounced at higher cumulative doses suggesting that there was a dose modification effect.

### 1.5.3 Younger Age (< 4 Years)

Children younger than 4 years at the time of diagnosis and initiation of chemotherapy have a higher likelihood of developing cardiac dysfunction (6). Up to 82% of children less than 4 years on chemotherapy, were found to have significantly thinner ventricles and elevated ventricular afterload.

### 1.5.4 Black Race

Race has been shown to be a risk factor for cardiac dysfunction in children with cancer. In a large retrospective review of 6493 children by Krischer et al., patients of black race had a 1.7 fold increased rick of cardiac dysfunction compared to non-blacks (12). They postulated the increased risk due to a two to three fold increased risk of idiopathic dilated cardiomyopathy amongst black race. However, more studies are needed to verify this hypothesis.

**1.5.5 Type of Malignancy**

Cancer in itself does contribute to cardiac dysfunction via several mechanisms including:

a) Direct tumour invasion of the myocardium or pericardium. This can occur with lympho- haematogenous spread to the heart, especially of lymphomas.

b) Leukemic infiltration that occurs in acute leukaemia. This usually involves the pericardium.

c) Tumour obstruction of the lymphatic drainage

Kariuki et al demonstrated that abnormal cardiac function in children with malignancies was actually attributable to the malignancies themselves (8). In this study, 80 children with cancer were compared to 80 controls without cancer. Sixteen percent (16%) of the cancer cases had abnormal cardiac function as determined by ECG and ECHO, compared to 8.8% of the controls. This outcome however was not statistically significant. This study did note that there was a higher occurrence of cardiac dysfunction in children with leukaemia as compared to those with solid tumours (18.2% vs 6.7%).

**1.5.6 Early Onset Cardiac Toxicity as a Risk Factor for Late Onset Cardiac Toxicity**

Early onset cardiac toxicity is strongly associated with development of late onset cardiac toxicity. In a study by Lipshultz et al.in children in 1997 (13),detection of cardiac injury using elevated troponin T during chemotherapy strongly correlated with significant left ventricular dysfunction as determined by echocardiography, 9 months later.

Prospective studies in adults have shown that evidence of early cardiac injury during high dose chemotherapy correlated well with development of significant cardiac dysfunction including overt clinical heart failure and even sudden cardiac death within a year of completion of treatment. In a large prospective study of 703 adults on high dose chemotherapy, Cardinale et al demonstrated that 44% of patients with an elevated cardiac troponin I during treatment, developed heart failure within 1 year of completion of treatment (14). In this study 84% of patients who had elevation in troponin I, had a significant cardiac event. They defined a cardiac event as either Death from a cardiac

cause, acute pulmonary oedema, overt heart failure or a reduction in Left ventricular ejection fraction(LVEF) of >25% from the baseline.

## 1.5.7 Other Potentially Cardiotoxic Drugs

Alkylating agents: The alkylating agents commonly used in our setting is cyclophosphamide and iphosphamide. These agents are associated with production of a cardiotoxic metabolite that causes endothelial damage, oedema and severe haemorrhagic myocarditis.

Cyclophosphamide causes clinical cardiotoxicity when administered in massive doses (120-240 mg/kg over 1-4 days), which is usually done when preparing for a bone marrow transplant. The prevalence of cardiotoxicity caused by these agents is about 28% (15).Amascarine- an acridine derivative with antileukemic effects and is potentially cardiotoxic

## 1.6 Diagnosis of Chemotherapy Induced Cardio-Toxicity

The cardiology committee of the children's cancer study group, primarily defines chemotherapy associated cardiac dysfunction as a deterioration in left ventricular function (16). Significant deterioration of function is suggested by:

- A fractional shortening of less than 29% or a left ventricular ejection fraction of less than 55%, on echocardiography.
- A left ventricular ejection fraction below 55% on radionuclide angiocardiography, or a decrease in radionuclide angiocardiographic Left ventricular ejection fraction with stress.

This definition reliably detects late cardiac changes at a point when cardiac function has irreversibly diminished. In light of this, it has become imperative to use more sensitive tests to detect cardiac injury early on, during cancer chemotherapy. Cardiac biomarkers have thus been proposed to be markers of choice in detection of early cardiac toxicity. Detection of early toxicity is important as it provides an excellent opportunity for the treating clinician to intervene and prevent further myocardial injury.

**1.7 Cardiac Troponin T as an Early Marker of Chemotherapy Induced Myocardial Injury**

Cardiac troponins are contractile proteins found in the cardiac myofilaments. The troponin protein complex regulates the contraction of the cardiomyocytes (17). The troponin complex consists of three subunits the Troponin T, Troponin I and Troponin C. Troponin C is a protein that binds to calcium ions. Troponin T binds to tropomyosin, thereby attaching the troponin complex to the actin thin filament. Troponin I binds to actin and decreases troponin C affinity for calcium, thus inhibiting actin–myosin interactions.

Damage of the cardiomyocytes results in release of Cardiac troponins from the intracellular compartment of the cardiomyocyte into serum. In the peripheral blood, Cardiac troponins levels start to rise 3-4 hours after myocardial injury, peak after 24 of myocardial injury and remain elevated for 10-14 days. (18, 19).

Cardiac troponins are cardio specific proteins that have historically been used in diagnosis of acute coronary syndromes in adults .They are the best known biomarkers for detecting myocardial injury. The serum levels of cardiac troponins have been shown to correspond well with the degree of myocardial infarct. The higher the serum troponin level the bigger the infarct size (19). Cardiac troponin T (cTnT) has been evaluated as a marker for detection of early chemotherapy induced cardiac toxicity.

In an animal model study, Herman et al demonstrated that loss of cTnT from damaged myocardial cells resulted in elevation of serum cTnT (20). In this quasi-experimental study, spontaneously hypertensive rats were injected with doxorubicin weekly for 12 weeks. The serum cTnT levels were analysed weekly and after 12 weeks, necropsies and cardiac histopathology and immunohistochemical staining of the heart muscle for cTnT was performed. They found that severe histopathologic myocardial lesions corresponded with higher serum levels of cTnT. The authors concluded that loss of cTnT was related to the myofibrillar lysis caused by doxorubicin.

Lipshultz et al demonstrated that elevation of cTnT occurred only in children with myocardial damage (13). In this study, serum cTnT levels of children receiving doxorubicin based chemotherapy regimens, were compared to levels of children undergoing cardiovascular surgery (positive controls) and those undergoing non-cardiovascular surgery (negative controls).Below are the most significant findings of this study:

a) In children without myocardial damage, the cTnT levels remained below the analytic detection level in all the groups.

b) CTnT levels were elevated in 25 %( 4/17) children after the first dose of chemotherapy.

c) CTnT elevations during treatment correlated with persistent left ventricular abnormalities, as detected by echocardiography 9 months later.

The positive predictive value and the negative predictive value of Cardiac troponins in detecting cardiac toxicity is 84% and 99% respectively (14). Thus troponins stratify cardiac risk in the very early phase long before impairment of heart function and symptoms develop. In an Italian study looking at left ventricular ejection fraction as predicted by early troponin release after high dose chemotherapy, Cardinale et al demonstrated that there was a close relationship between the peak value of cardiac troponin I and the degree of late LVEF reduction (21). In this study, 29% of patients who had an elevated troponin I level had LVEF of less than 50% compared to none (0%) of those who had an undetectable troponin level. The author concluded that cardiac troponin I was a sensitive and reliable marker of minor cardiac damage with relevant clinical and prognostic implication.

In a paediatric study in 2012, Lipshultz et al demonstrated that increased cTnT in the 1st 90 days of treatment with chemotherapy was associated with reduced Left ventricular mass and Left ventricular end diastolic posterior wall thickness, 4 years after completion of chemotherapy (22). In another study in 2004 Lipshultz et al demonstrated that troponins were sensitive and specific markers of myocardial injury (23). In this randomised control trial, children with ALL were randomised to either receive

doxorubicin alone or doxorubicin plus dexrazoxane, as part of their chemotherapy regimens. Dexrazoxane chelates iron and thus reduces the production of free oxygen radicals produced during doxorubicin metabolism, therefore reducing the cardiac toxicity of doxorubicin. The incidence of myocardial injury was reduced in the doxorubicin/dexrazoxane group when compared to the doxorubicin group (21% Vs 50%).

In a study done in Turkish adult patients, Kilicap et al demonstrated that elevation in cTnT after chemotherapy was associated with diastolic dysfunction as detected by echocardiography (24).In this study, post treatment LVEF and FS did not change from base line. There was a strong association between elevated cTnT levels and the cumulative doxorubicin dose received.

Finally, in a recent study of Chinese survivors of childhood malignancies published in 2013, elevated cardiac troponin T was associated with Left ventricular systolic and Diastolic dysfunction, 5 years after completion of chemotherapy (25). Higher serum cTnT levels were associated with use of higher cumulative doxorubicin doses, leukemic relapse and stem cell transplantation. In this study, polymorphisms of the CYBA-rs 4673 gene (encoding the Multi Drug resistance transport protein), was associated with higher levels of serum cTnT.

The table 1.3 below summarises the above studies on utility of cardiac troponin T in detection of chemotherapy induced   cardiac injury

**Table 1.3 Summary of Cardiac Troponin studies**

| STUDY AUTHOR,STUDY SETTING,SAMPLE SIZE | STUDY DESIGN | PREVALENCE OF ELEVATED TROPONIN LEVEL | MAIN OUTCOMES |
|---|---|---|---|
| Herman et al[20] America.n=19 | Quasi-experimental (animal study) | 75% | Increase serum cTnT due to myofibrillar lysis caused by Adriamycin. 50% mortality in rats given doxorubicin |
| Lipshultz et al[13] America. n=51 | Prospective cohort | 66% | Elevated cTnT associated with LV dysfunction 9 months later |
| Cardinale et al[14] Italy.n=703 | Prospective cohort | 30% | Positive Predictive Value of cTnI-84% Negative predictive value of cTnI-99 %. |
| Cardinal et al.[21] Italy. n=204 | Prospective cohort | 32% | Close relationship between elevated cTnI and degree of LVEF reduction. |
| Lipshultz et al.[23] America. n=158 | RCT | 35% | Two fold reduction in myocardial injury, when dexrazoxane/doxorubicin combination was used |
| Lipshultz et al [22] America. n=156 | RCT | 32% | Elevation in cTnT in 1st 90 days associated with poor LV function 4 years later. |
| Kilicap et al [24] Turkey. n=40 | Prospective cohort | 34% | CTnT elevation associated with diastolic dysfunction and higher cumulative doxorubicin dose. |
| Yui-Fai Cheng [25] China. n=100 | Cross-sectional study with a comparative arm. | 19% | Elevation of cTnT associated with worse LV systolic and diastolic function and higher cumulative doxorubicin dose in those with elevated cTnT |

**1.8 Strategies for Preventing Chemotherapy Induced Cardiac Dysfunction**

Use of cardiac troponin T allows the clinician to detect subclinical myocardial injury. This provides one with an excellent opportunity to intervene and prevent subsequent cardiac morbidity and mortality. The interventions that can be used include:

- Dose reduction of potentially cardio toxic drugs- This is aimed at reducing peak plasma levels of potentially cardiotoxic agents and thus preventing subsequent cardiac dysfunction. Several studies have shown that a higher cumulative dose of anthracyclines is associated with an increased risk of cardiac toxicity. (5,6,9,10,11).

- Altering the mode of drug delivery- continuous intravenous infusion of doxorubicin given over 48-96 hours had been shown to reduce the incidence of biopsy confirmed myocardial injury, when compared to a bolus intravenous infusion (26). Continuous infusions reduce the peak plasma levels without affecting the oncologic efficacy of the drug. This reduces the occurrence of cardiac   toxicity while maintaining the anti-tumour efficacy of the drug.

- Use of cardio-protective agents such as dexrazoxane- Dexrazoxane chelates iron, thus preventing the formation of doxorubicin-iron complexes that are toxic to the myocardium. In a randomised control trial, use of dexrazoxane/doxorubicin combination significantly reduced the occurrence of myocardial injury, as detected by elevated cardiac troponin T (22, 23).

- Use of safer anthracycline formulations such as liposomal doxorubicin- Use of liposomal doxorubicin has been shown to reduce the incidence of cardiac toxicity. Liposomal encapsulation of the drug modifies the pharmacokinetics and tissue distribution of the drug, without altering its anti-tumour properties (27).

- Use Angiotensin converting enzyme inhibitors and Beta blockers- In a randomised control trial, prophylactic Carvedilol (beta blocker) was shown to preserve left ventricular ejection fraction in patients who are receiving anthracycline chemotherapy (28). Use of enalapril prophylactically has also been shown to prevent development of anthracycline induced cardiomyopathy, when given to patients receiving chemotherapy (29). The protective mechanisms are

due to the drugs' effect on the haemodynamic status and prevention of Left ventricular remodelling.

## 1.7 Study Justification

The current prevalence of myocardial injury in African children receiving cancer chemotherapy, as detected by elevated cardiac troponin T, is unknown. This will be the one of the first African studies to assess the utility of a cardiac biomarker, in detecting subclinical myocardial injury in children on cancer chemotherapy.

Detection of early cardiac toxicity in children receiving cancer chemotherapy provides an excellent opportunity to intervene thus preventing dilated cardiomyopathy, congestive heart failure and even death in these children. Cardiac Troponin T has been shown to be more sensitive marker and has higher positive and negative predictive values, as compared to echocardiography, which is the current standard of care. This biomarker is also cheaper than echocardiography. Its higher negative predictive value also allows for exclusion of patients from long term monitoring and serial echocardiography, thus justifying its use and lowering the cost to the patient. Cardiac troponin T is also easy to interpret and unlike echocardiography, does not require specialised personnel, to interpret.

## 1.8 Study Utility

If good diagnostic utility is demonstrated, a case can be made for Kenyatta National hospital to institutionalise cardiac troponin T for monitoring of children receiving cancer chemotherapy. This study may also be used to guide paediatric oncologists in drawing up monitoring protocols, for children on cancer chemotherapy in our setting.

The results of this study may be used as a baseline for other follow-up prospective studies evaluating the utility of cardiac biomarkers in detecting myocardial injury in African children with malignancies.

# CHAPTER TWO: STUDY OBJECTIVES AND RESEARCH QUESTION

## 2.1 Research Question

What is the prevalence of myocardial injury, as determined by elevated cardiac Troponin T, in children receiving cancer chemotherapy, at Kenyatta National hospital?

## 2.2 Primary Objective

1) To determine the prevalence of myocardial injury, as determined by elevated cardiac troponin T, in children receiving cancer chemotherapy at Kenyatta National Hospital

## 2.3 Secondary Objective

2) To determine the clinical and demographic factors associated with elevated cardiac troponin T levels in children receiving cancer chemotherapy at Kenyatta National Hospital including cumulative doxorubicin dose, age and gender.

3) To determine the association between elevated cardiac troponin T levels and Left ventricular dysfunction (reduced fractional shortening) in children on cancer chemotherapy at Kenyatta National Hospital.

# CHAPTER THREE:METHODOLOGY

## 3.1 Study Design

Hospital based Cross-sectional study.

## 3.2 Study Area

The study was carried out on patients in the Kenyatta national hospital (KNH) general paediatric wards and the paediatric oncology ward.

Kenyatta national hospital in a tertiary institution and is Kenya's main national hospital. It is located in Nairobi, the capital city of Kenya. It is a teaching hospital for the University of Nairobi and is the major referral hospital for all paediatric cancer patients in Kenya. Approximately 7-10 children with malignancies are referred every month.

## 3.3 Study Population

The population of interest was the in-patient children between the age of one month and 18 years admitted with a diagnosis of cancer at Kenyatta national Hospital and whose parents or guardians gives a signed consent.

## 3.4 Study Site

The study site included the paediatric oncology ward (1E), and the general paediatric ward 3A, 3B, 3C and 3D.
The Paediatric oncology ward (ward 1E) is a specialised paediatric oncology ward which holds an average of twenty five (25) to thirty (30) patients. A vast majority of the patients in this ward are on management for leukaemia, lymphomas and solid tumours. This ward only admits children under the age of thirteen (13) years.

Due to the high number of children with malignancies, some of the children are admitted to the general paediatric wards which are ward 3A, 3B, 3C and 3D.  Each of these wards hold an average of 15-20 children. Most of the children in the general wards are on management for hematologic and solid tumours. The general paediatric wards only admit children under the age of thirteen (13).

## 3.5 Study Period

The study period was July 2016 to December 2016.

## 3.6 Inclusion Criteria

Children between 1 month and 18 years old who had a diagnosis of cancer and who were currently receiving chemotherapy.

## 3.7 Exclusion Criteria

Children with pre-existing congenital or acquired heart disease Including rheumatic heart disease, as determined by echocardiography.

## 3.8 Sample Size Determination

Based on the primary objective, Fischer's formula for sample size calculation was used:

$$N = \frac{Z^2_{1-/2} P(1-P)}{d^2}$$

- n=minimum sample size
- Z-1.96 is the normal deviate corresponding to a confidence interval of 95% confidence interval
- $\alpha$ ≈0.05 level of significance
- d=0.075 level 0f precision
- P=estimated prevalence of elevated cardiac troponin T in children receiving cancer chemotherapy. Based on an Asian study in childhood cancer survivors, the prevalence of elevated cardiac troponin T was 19 %( 25).

Thus: N= 1.962 X 0.975 X 0.19 X 0.81

                0.075

N = 100

## 3.9 Study Outcomes

The outcome of this study was to determine the prevalence of myocardial injury. Myocardial injury was defined as:

Cardiac Troponin T level greater (>) than 0.014 ng/ml

Or

Echocardiographic evidence of Left ventricular Fractional shortening of less (<) than 29%.

## 3.10 Study Procedure

### 3.10.1 Patient Selection

Patients who met the above inclusion criteria and whose parents or guardian gave consent were sequentially recruited from the paediatric oncology ward (ward 1E) and the general paediatric wards (ward 3A, 3B, 3C, 3D) until the required minimum sample size of 100 patients was attained.

The recruitment was done by the principal investigator on a daily basis, until the minimum sample size was attained. Recruitment commenced at the general paediatric wards (wards 3A, 3B, 3C, 3D) and then progressed to the paediatric oncology unit (ward 1E). Any child with pre-existing symptomatic congenital heart disease or rheumatic heart disease was excluded.

### 3.10.2 Study Procedure

1. The patients' medical records were reviewed to confirm that a diagnosis of cancer had been made. Typically this diagnosis was made after evaluation of a Bone marrow aspirate, Fine needle aspirate, excisional or incisional biopsy and by use of various biochemical markers including flow cytometry, by a specialist pathologist. The pathology report was thus reviewed by the investigator to confirm the type of cancer diagnosed.

2. A full physical examination was be carried out. The patient data including the age, gender, anthropometric measurements, the current chemotherapy regimen, the cumulative anthracycline dose, the haemoglobin level, the cumulative alkylating agent dose and history of irradiation, were extracted from the patient's medical records and entered into a patient data collection sheet. (Appendix I).

3. The patients then underwent a 2-D echocardiography. This was done at the patient's bed side it was carried out by a paediatric cardiologist, in the presence of the investigator. The First 2-D ECHO was done prior to chemotherapy infusion. Echocardiography was conducted using uniform methodical protocol based on the set guidelines. The 2-D echocardiography was carried out using an echocardiography machine LOGIQ 500 Model, with frequency of 33/02.5 MHz.This machine was manufactured by GE Yokogama medical systems Ltd. Tokyo, Japan.

Sub costal, parasternal, apical and suprasternal views were used. The modalities of echocardiography used are the two-dimensional real time-mode, pulse-wave Doppler and continuous wave Doppler echocardiography. 2D-real time echocardiography was used to assess the cardiac measurements, visual contractility and any abnormal findings like cardiac masses. M-mode echocardiography was used to assess the relative chamber sizes and to calculate the indices of cardiac contractility. Spectral pulse wave Doppler with sample specimen taken at the tips of the mitral valve leaflets was used to assess the diastolic function.

Fractional shortening is the percentage size reduction of the left ventricle at end of systole. It is determined using the M-mode echocardiography. It is computed by the machine using this formula:

$$\frac{LVEDD - LVESD}{LVEDD} \times 100$$

A fractional shortening of <29% was considered abnormal.

Diastolic function was measured by peak early velocity (E wave), peak atrial velocity (A wave), E wave/A wave ration (E/A), E deceleration and isovolumetric relaxation time (IVRT).

Patients with evidence of congenital heart disease or rheumatic heart disease were excluded from the study at this point.

All the information regarding the ECHO results were recorded in a data collection sheet. (Appendix III).

4. Twenty four (24) hours after chemotherapy infusion a blood sample was drawn from the patient's antecubital fossa. The puncture site was first cleaned with a spirit swab and a 21 gauge needle was used to draw one (1) millilitre of blood, which was put in a heparinised vacutainer. The collection of the blood sample was done by the principal investigator. The blood sample was then be stored in a cooler box and transported to the lab immediately for analysis of the serum cardiac troponin T level. The principal investigator was responsible for the collection and transportation of the blood specimens to the laboratory.

Upon arrival to the laboratory, the cardiac troponin T level was measured using the Elecsys troponin T STAT Immunoassay, manufactured by Roche Diagnostics. The lower limit of detection of this assay is 0.003 ng/ml. This assay utilises electro-chemiluminesence to quantify the serum cardiac troponin T level. An abnormal value was defined as any detectable level of cardiac troponin T, that is, any level above 0.014 ng/ml. The laboratory that conducted the analysis is accredited by the Kenya National Accreditation system (KENAS) and is also internationally certified (ISO 15189:2012 certified).Internal quality control checks are run daily prior to sample analysis and external quality control of this laboratory is under the THISTLE system.

Disposal of the biological specimens followed International standard operating procedures. Immediately after analysis of the specimen, the specimen containers with the blood specimen, were decontaminated using 10% sodium hypochlorite solution (bleach) for twenty (20) minutes. The containers bearing the biological specimen were then wrapped in appropriate biohazard bags and incinerated. The chief laboratory technologist was responsible for the processing and disposal of the biological specimens.

5. The patient then had a second echocardiography 24 hours after chemotherapy infusion. This was done soon after the above blood sample was drawn. All the parameters explained above (in no. 3) were evaluated and the information was recorded in a data collection sheet. (Appendix II)

**3.11 Study Methodology Flow Chart**

Patients assessed for eligibility: patient less than 18 years with a diagnosis of cancer = **113 children** assessed

3 Participants excluded prior to first ECHO:

- 1 Chemotherapy halted as remission achieved
- 2 died

**110** participants had first 2-D ECHO done before scheduled chemotherapy infusion.

10 excluded prior to cTnT sampling.

- 1 had congenital heart disease
- 1 chemotherapy halted due toxicity.
- 4 died prior to cTnT sampling
- 4 discharged before cTnT sampling

**100** participants had cTnT sampling done 24 hours after their scheduled chemotherapy, 58 children had second ECHO done.

Analysis of results of 100 participants. Myocardial injury defined as cardiac troponin T >0.014 ng/ml or FS <29% on echocardiography.
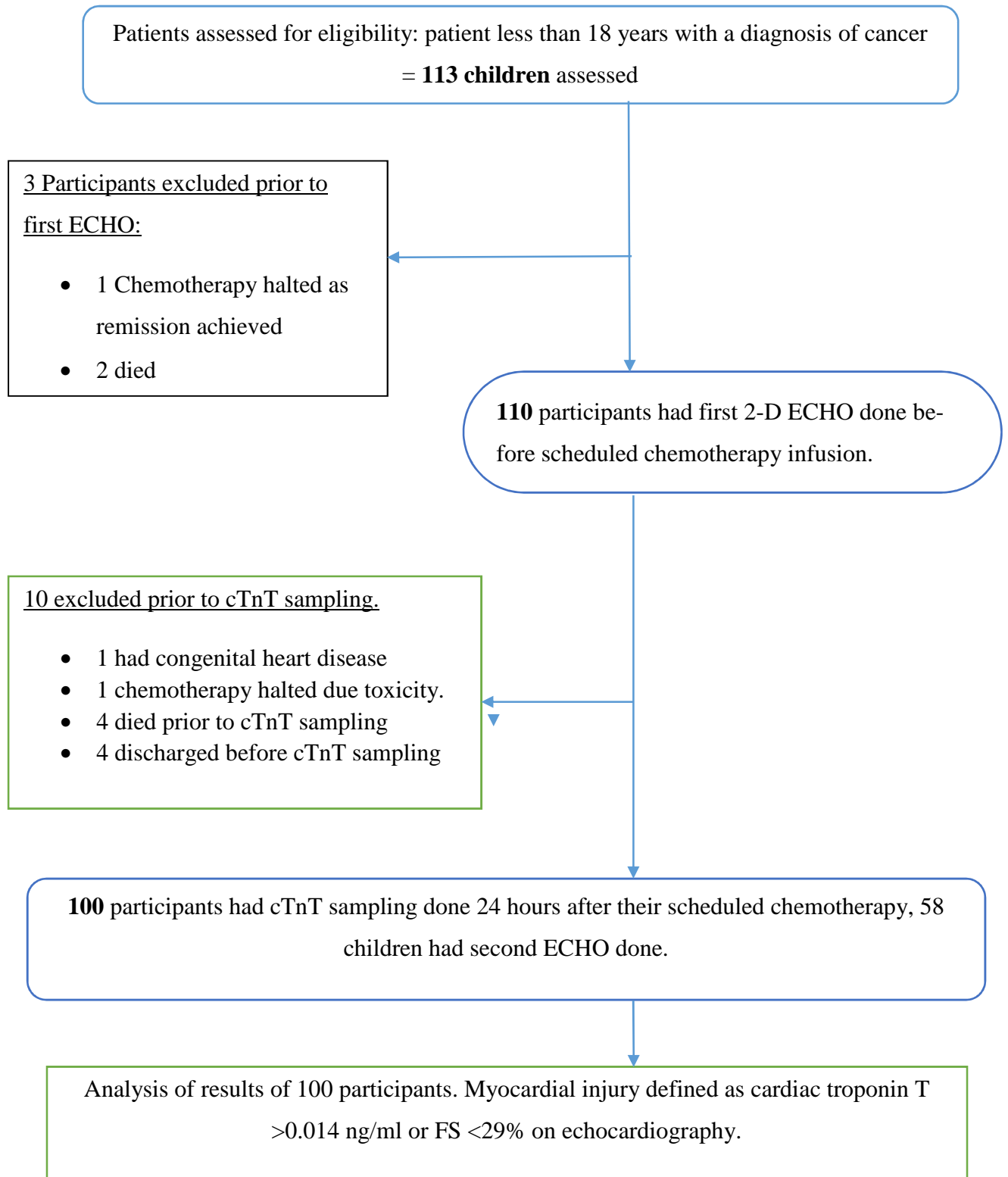
**Figure 3.1: Study Flow Chart**

**3.12 Ethical Considerations**

1. The study was undertaken after approval by the Department of Paediatrics, University of Nairobi (UON) and the Ethical and scientific committee Kenyatta National hospital (KNH).

2. Informed consent was sought from the parent or guardian (appendix III/Kiambatanisho III). The parent or guardian was allowed to withdraw the patient at any stage without any obligation and this did not compromise the management of the child.

3. No patient suffered delay in treatment by inclusion into this study and emergency care and resuscitation took precedence over any other procedure.

4. The cost of the tests to be conducted in this study were be borne by the investigator. The patient did not incur any cost by participating in this study.

5. The results obtained, both the Echocardiographic report and the cardiac troponin T level, were relayed to the patient/guardian and their primary doctor.

6. When a diagnosis of cardiac disease was made, the patient/Guardian was accorded psychosocial support and was counselled about the findings. Subsequent counselling services were also provided to the patient/guardian to mitigate any psychological distress that may have arisen in view of the diagnosis of cardiac disease. The patient was also be linked to a paediatric cardiologist for follow up and management of the cardiac disease.

7. All information obtained from the patient, including the results of the tests to be conducted in this study, were treated with strictest confidence. No patient information was released to any unauthorised third party without prior written approval of the study institution or the Ethics and Research committee.

**3.13  Data Management**

Data emanating from this study was entered into a patient data sheet and then recorded in a computer data base, SPSS version 23.0. Analysis of this data was done using the STATA.

Descriptive analysis was done using means (SD) and medians (IQR) for continuous variables while counts and percentages for categorical variables. Bivariate analysis was done using chi squares for the categorical variables and t-tests or median tests as appropriate reporting the p values. Univariable and multivariable logistic regression analysis was done to demographic and clinical characteristics associated with an abnormal troponin level in the patients. Variables which exhibited multicollinearity were excluded from the final model. Odds ratios, p values and respective 95% confidence intervals were also presented.

# CHAPTER FOUR: STUDY RESULTS

During the study period between July-December 2016, a total of 113 children were assessed for enrolment into the study. Thirteen (13) children were excluded .One hundred (100) children were included in the final analysis as shown in the figure 2.0 on page 20.

## 4.1 Characteristics of the Study Population

**Table 2.1: Characteristics of the Study population**

| CHARACTERISTICS | FREQUENCY (%)/ MEDIAN (IQR) |
|---|---|
| Male | 64 (64%) |
| Age (mo.) | 53 (35-84) |
| Weight (kg) | 15 (12-19) |
| Malignancy group. | |
| • Leukaemia | 29 (29%) |
| • Lymphoma | 14 (14%) |
| • Solid tumour | 57 (57%) |
| Malignancy Type: | |
| • Nephroblastoma | 33 (33%) |
| • Acute Lymphocytic leukaemia | 27 (27%) |
| • Non-Hodgkin lymphoma | 10 (10%) |
| • Rhabdomyosarcoma | 9(9%) |
| • Hodgkin Lymphoma | 4(4%) |
| • Others | 17(17%) |
| Malignancy stage (for lymphoma and solid tumours only): | |
| • Stage 1 | 21 (30%) |
| • Stage 2 | 6 (8.5%) |
| • Stage 3 | 22(31.4%) |
| • Stage 4 | 21(30%) |
| Treatment Duration (mo.) | 3 (0.25-8.5) |
| Exposed to Anthracyclines. Yes No | 77 (77%) 23(23%) |
| Anthracycline Dose category (mg/m$^2$) <50 51-100 101-175 >175 | 37 (37%) 29 (29%) 17(17%) 17(17%) |
| Exposed to alkylating agents. Yes No | 61 (61%) 39(39%) |

Majority of the children were male, 64 (64%) and 36(36%) were female with a male to female ratio of 1:1.8. The median age was 53 months (IQR=35-84). Eight participants (8%) were wasted with a Weight/height Z score of less than -3. Twelve participants (12%) were stunted with a Height/Age Z score of less than -3, and ten participants (10%) were underweight with a Weight/Age Z score of less than -3.

The spectrum of malignancies was as shown in the table 6.0 above. The commonest malignancy type was Nephroblastoma with a third of the study population having this diagnosis, 27 participants (27%) had ALL and 10(10%) had a diagnosis of NHL. In terms of tumour stage, 43 patients (61.4%) with solid tumour and lymphomas had advanced disease (stage 3 and 4). Tumour staging was only done for lymphomas and solid tumours since leukaemias are traditionally not staged.

The median duration of treatment was 3 months (IQR=1-8.5 months). Seventy seven children (77%) were exposed to an anthracycline (mainly Adriamycin) with a median cumulative Adriamycin dose of 90.5 mg/m2 (Range 0-550 mg). Of note 37 participants (37%) had a cumulative anthracycline dose of $<50$ mg/m$^2$ and 17(17%) had a cumulative anthracycline dose of $>175$ mg/m$^2$. Sixty one percent (61%) of the study population was exposed to an alkylating agent with a median alkylating agent dose of 950 mg/m$^2$ (Range of 0-9900 mg). The alkylating agent mainly used was cyclophosphamide.

## 4.2 Descriptive Statistics of the Main Study Outcomes

**Table 4.2: Descriptive Statistics of the main outcomes**

| MAIN OUTCOME. | FREQUENCY (%) |
|---|---|
| cTnT level: | |
| • Elevated | 32(32%) |
| • Normal | 68(68%) |
| Echocardiographic outcome Fractional shortening (FS) | |
| Abnormal | 9(9%) |
| Normal | 91(91%) |

As shown in table 4.2 above, 32% of the study population had elevated cTnT, 9% had an abnormal fractional shortening on echocardiography. These results are further described below.

## 4.3 Objective 1: Prevalence of elevated Cardiac Troponin T

The proportion of participants with elevated cTnT levels was, 32% (95%CI: 23.67% - 41.66%). The figure 4.1 shows the proportion of participants with abnormal Vs normal cTnT.
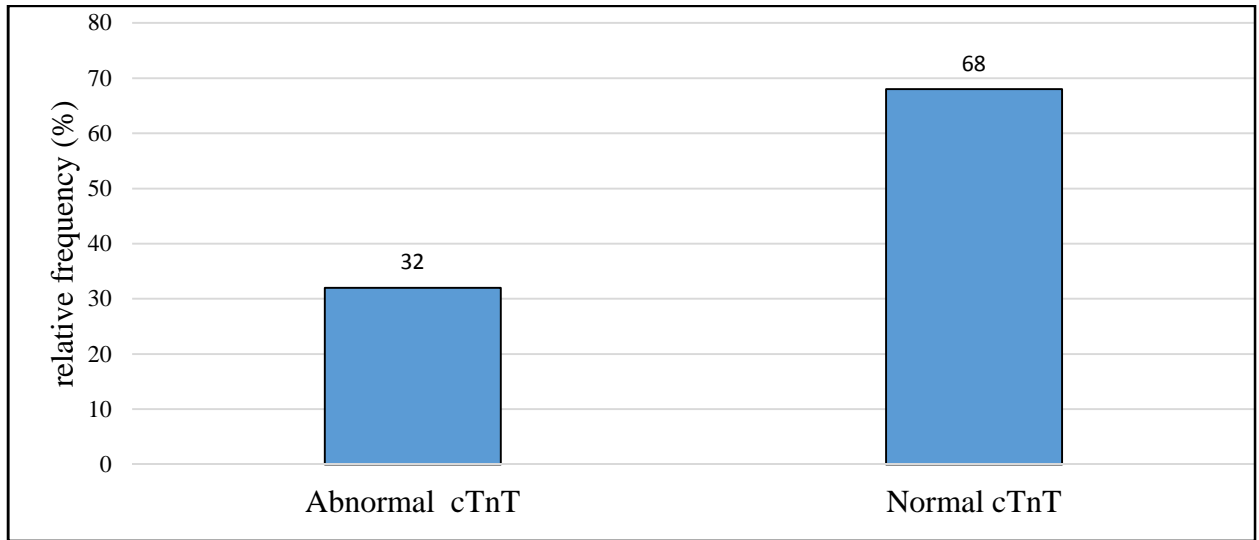


**Figure 4.1: Bar Graph showing the proportion of participants with abnormal cTnT**

The median Cardiac Troponin T level was 0.0085 ng/l (range of 0.003-0.144 ng/l). Figure 4.2 below shows the cTnT levels amongst the 100 study participants.
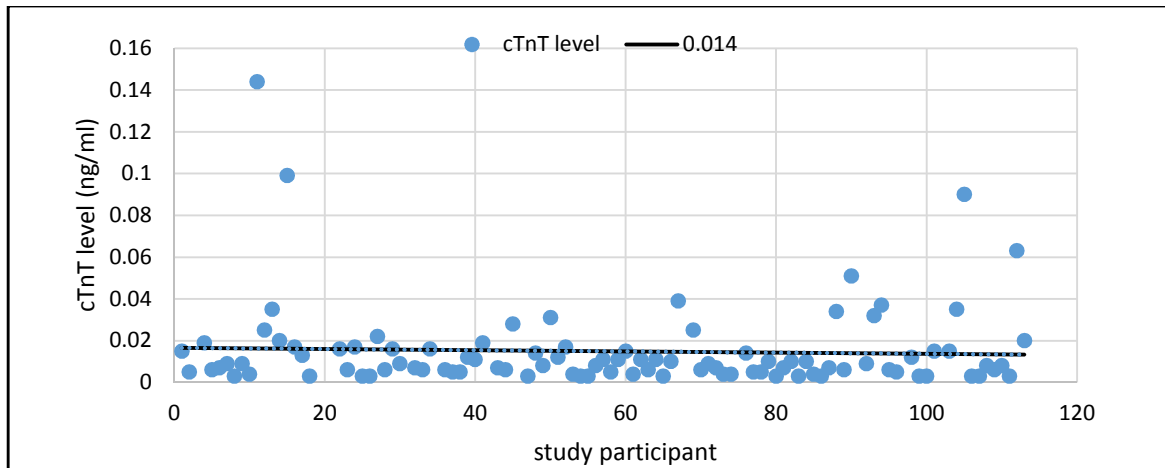


**Figure 4.2: Scatter plot showing cTnT levels amongst study participants**

## 4.4 Objective 2: Factors Associated with an Elevated cTnT

### Table 4.3: Summary of univariate analysis of factors associated with elevated cTnT

| Characteristics | Elevated cTnT n (%) n=32 | Normal cTnT n (%) n=68 | OR (95% CI) | P value |
|---|---|---|---|---|
| Median Age (mo.) | 44 (22-80) | 60 (37-89) | 0.99(0.97-1.003) | 0.08 |
| **Gender.**<br>Female (IQR)<br>Males | 15( 46.9)<br>17 (53.1) | 21(30.9)<br>47 (69.1) | 2.098 (0.877-5.020) | 0.12 |
| WHO W/H Z score (<-3) | 2 (6.5) | 6 (9.2) | 1.037 (0.404-2.660) | 0.90 |
| **Malignancy group.**<br>Solid tumour<br>Leukaemia<br>Lymphoma | 23(71.9)<br>3 (9.4)<br>6 (18.8) | 34 (50)<br>26 (38.2)<br>8 (11.8) | - | 0.039<br>0.012 |
| **Malignancy type.**<br>Nephroblastoma<br>ALL<br>NHL<br>Rhabdomyosarcoma<br>others | 16(50)<br>3(9.4)<br>5(15.6)<br>2(6.2) | 17(25)<br>24(35.3)<br>5(7.4)<br>7(10.3) | - | 0.013 |
| **Malignancy stage:**<br>Stage 1<br>Stage 2<br>Stage 3<br>Stage 4 | 8(29.6)<br>1(3.7)<br>10 (37)<br>8(29.6) | 13 (30.2)<br>5 (11.6)<br>12 (27.9)<br>13(30.2) | -<br>2.69(0.26-27.80)<br>4.17(0.41-41.78)<br>3.077(0.30-31.33) | -<br>0.40<br>0.22<br>0.64 |
| **Exposure to anthracy-clines:**<br>Yes<br>No | 25 (78.1)<br>7(21.9) | 52(76.5)<br>16(23.5) | 0.94(0.34-2.60) | 0.92 |
| **Cumulative anthracycline dose (mg/m2)**<br><50<br>50-100<br>100-175<br>>175 | 10 (31.2)<br>11(34.4)<br>3(9.4)<br>8(25) | 27(39.5)<br>18 (26.5)<br>14(20.6)<br>9(13.2) | -<br>1.65(0.58-4.68)<br>0.58(0.13-2.44)<br>2.4(0.72-7.96) | 0.34<br>0.45<br>0.15 |
| **Exposure to alkylating agents:**<br>Yes<br>NO | 22 (68.8)<br>10 (31.2) | 39 (57.4)<br>29 (42.6) | 0.64 (0.26-1.56) | 0.28 |

The proportion of males with elevated cTnT compared to females with an elevated cTnT was, 17 (53.2%) vs 15 (46.9%), p=0.120. The median age of patients who had elevated cTnT was lower when compared to those with normal cTnT, 44 months (IQR=22-80) 60 months (IQR=37.5-89.5), p=0.0766.

The proportion of participants with solid tumours and elevated cTnT, compared to non-solid tumour cases with elevated cTnT was 23 (71.9%) Vs. 9 (28.2%) and this was statistically significant p=0.039. The proportion of participants with a diagnosis of Nephroblastoma with elevated cTnT compared to those with all other tumour types and elevated cTnT was 16(50%) vs. 16(50%) and this was statistically significant p= 0.013. The proportion of participants with stage 4 disease and elevated cTnT, compared to those with stage 1 disease and elevated cTnT was similar 8(29.6%) vs. 8(29.6%) and this was not statistically significant, OR 3.011( 95% CI: 0.3-31.1),p=0.64.

The proportion of participants exposed to anthracyclines with elevated cTnT, compared to those not exposed to anthracyclines with elevated cTnT was 25(78.1%) vs 7(21.9%), though this was not statistically significant OR 0.984 (95% CI: 0.34-2.60), p=0.854.

The cumulative Adriamycin dose was further categorised into 3 groups and we compared the risk of having an elevated cTnT per each group. The reference group for this comparison was the < 50mg/m2 group. Patients who received more than 175mg/m2 of doxorubicin had over two fold increase in the odds of having abnormal troponin level, OR =2.4 (95% CI: 0.725-17.946), p= 0.152 however this was not significant.

The proportion of participants exposed to cyclophosphamide with elevated cTnT, compared to those not exposed to cyclophosphamide with elevated cTnT was 22( 68.8%) vs.10 (31.2%) though this was not significant, OR 0.64 (95% CI:0.26-1.56),p=0.28.

## 4.5 Multivariate Analysis

In order eliminate confounders, we looked cumulative anthracycline dose and malignancy type (Nephroblastoma) and put the logistic regression model below:

**Table 4.4: Logistic regression of factors associated with elevated cTnT**

| Outcome: cTnT(Elevated vs. Normal) | Odds ratio (95% CI) | P-value |
|---|---|---|
| Malignancy type: Nephroblastoma | 3 (1.23-7.26) | 0.015 |
| Cumulative Adriamycin Dose (mg/m2) >175 | 10.76(1.18-97.92) | 0.035 |

Participants with a diagnosis of Nephroblastoma had a 3 fold significant increase in the odds of having an elevated cTnT compared to those with other malignancy types, OR 3 (95% CI: 1.23-7.26), p=0.015. Malignancy group of solid tumour, which was a significantly associated with an elevated cTnT was excluded from the logistic regression model because of collinearity. Participants who received more than 175mg/m2 of doxorubicin had a more than tenfold increase in the odds of having an elevated cTnT level, OR=10.76 (95% CI: 1.182-97.92), p=0.035. This finding was statistically significant.

## 4.6 Objective 3: The Association between Elevated cTnT and Echocardiography (FS)

Nine (9 %) study participants exhibited abnormal Fractional shortening (95%CI: 4.38% - 15.9%) as shown in the table 7.0 above. The association between elevated cTnT and FS, is shown in tables 10.0 below and further described below.

**Table 4.5: Association between elevated cTnT and FS**

| | Abnormal FS n (%) | Normal FS n (%) | P value. |
|---|---|---|---|
| Elevated cTnT | 2 (6.25) | 30 (93.25) | 0.775 |
| Normal cTnT | 7(10.2) | 61(89.7) | |

The proportions of participants with abnormal FS and elevated cTnT compared to those with abnormal FS and normal cTnT was 2(6.25%) vs 7 (10.2%), this was not statistically significant p=0.775. Thus there was no association between an elevated cTnT and an abnormal Fractional shortening.

## 4.7 Other Echocardiographic Findings

**Table 4.6: Summary of other Echocardiographic findings**

| Abnormality. | Frequency (%) |
|---|---|
| Tricuspid regurgitation | 25 (25%) |
| Pulmonary hypertension | 5 (5%) |
| Diastolic dysfunction | 13 (13%) |
| Pericardial effusion. | 3 (3%) |

In addition to left ventricular function other significant echocardiographic findings included Diastolic dysfunction, tricuspid regurgitation, pulmonary hypertension, pericardial and pleural effusions, as shown in table 9.0 above. Of the study participants 13 (13%) had diastolic dysfunction, 10 (76%) of these had the restrictive type and 2 (26%) of these had the pseudo-normalised type.

Twenty five participants (25%) had tricuspid regurgitation as determined by an elevated pulmonary pressure gradient (Range 5-55 mmHg) and 5 (20%) of these participants had Pulmonary hypertension with Pulmonary pressure gradient of greater than 25 mmHg.Three participants (3%) had pericardial effusion on echo. Only 3 (3%) had pleural effusion on echocardiography.

## CHAPTER FIVE: DISCUSSION

### 5.1 Discussion

The mainstay of management of most paediatric malignancies is chemotherapy. Use of chemotherapeutic agents has increased the survival of children with cancers. The use of some of these agents is however limited by their toxicity profile, especially cardiac toxicities. It is thus essential to detect early cardiac toxicities of cancer chemotherapy so as to prevent occurrence of late cardiac toxicities, including dilated cardiomyopathy. Cardiac troponins are the best known molecular markers of myocardial injury and detect subclinical myocardial injury long before echocardiographic changes are appreciated (13, 14, and 22).

The prevalence of elevated cTnT in children on cancer chemotherapy was 32% (CI 23.67-41.66%). This represents about a third of the study participants and it is similar to what has previously been documented in Caucasian children and adults. In a study by Lipschultz et al, 35% of children on cancer chemotherapy for treatment of ALL, had an elevated cTnT (23). Similar results have been documented in adult populations by Cardinale et al where the point prevalence of elevated cTnT raged between 30%-32% (13, 15, 21).However, amongst a Chinese population of childhood cancer survivors, Yui-Fai Cheng described a prevalence of only 19% (25). It is worth noting that most of these studies were prospective cohort studies that evaluated cTnT serially, while we only had a one-time 24 hour post-infusion evaluation of the serum cTnT. We speculate therefore, that our study could have under-estimated the prevalence of myocardial injury given the nature of the study design

This study did show that exposure to an anthracycline was significantly associated with elevated cTnT. At a cumulative Adriamycin dose of $> 175$ mg/m$^2$ there was a tenfold increased risk of having an elevated cTnT, OR 10.76 (95% CI 1.187-97), p=0.035. Anthracyclines are known to cause cardiac toxicity and this fact has been well documented. This study did demonstrated subclinical cardiac toxicity, occurring at a relatively lower dose of Adriamycin exposure, unlike previous studies. Shiroya et al did demonstrate that at a dose of $> 200$mg/m2, there was a 4.4 increased risk of myocardial

injury in African children (9). Lipshultz et al demonstrated that at a dose of > 228 mg/m2, 65% of children exposed to anthracyclines developed late cardiac toxicities as determined by echocardiography (6). We thus hypothesise that the use of a sensitive biomarker in a population of African children can explain this finding. The results of this study further demonstrates that cTnT can be used for detection of anthracycline associated subclinical myocardial injury, as has been previously documented (22, 23, 24).

Solid tumours, especially Nephroblastoma, was significantly associated with elevated cTnT OR 3 (1.23-7.26), p=0.015. Nephroblastoma does cause cardiac injury since intracardiac tumour extension has been known to occur in these tumours. We did demonstrate intracardiac tumour masses in only one child who was eventually excluded from the study. In our setting, children with advanced disease do receive higher doses of anthracyclines in their protocols and 67% of children with Nephroblastoma had advanced disease. We thus speculate, there could have been residual confounding between the tumour and the drug dose. Also since we did not have a baseline cTnT for comparison, it will be difficult to speculate as to whether this occurrence is purely as a result of the tumour or the use of chemotherapeutic agents.

Other factors that were explored included age, gender and nutritional status. There was a slight decrease in the odds of having an elevated cTnT for every unit age increase in age, OR 0.98 (95% CI 0.972-1.003), but this was not significant. Younger children (< 4 years) are at a higher risk of chemotherapy induced cardiac toxicity (6). Female patients had a higher odds of elevated cTnT levels as compared to males, OR 2.283 (95% CI 0.864-6.02), though this was not statistically significant. Being female has been associated with an increased risk of developing chemotherapy induced cardiac toxicity (11). Nutritional status was not associated with elevated cTnT. This is similar to what has been described in previously (9).

Only 9% of the study participants had echocardiographic evidence of myocardial injury. This is lower than was previously described. A study done by Shiroya et.al. in Kenyan children on cancer chemotherapy, found that 29% of these children had

echocardiographic evidence of myocardial injury (9). When compared to that study, the study participants in our study had a shorter duration of treatment and a lower cumulative anthracycline dose. This could explain the difference in the study results.

Lastly, this study did not find any association between elevated cTnT and abnormal echocardiographic parameters. Troponin elevation occurs way before anatomical changes can be appreciated by echocardiography. In a longitudinal cohort study, Lipshutlz at al described cTnT elevation occurring 9 months prior to echocardiographic changes (20). Our study design could thus explain this finding, given that our study was a cross-sectional study.

## 5.2 Strengths of the Study

The study design was appropriate to answer the study question. The study participants included in the final analysis had an echocardiogram and a cTnT sample result.

## 5.4 Study Limitations

Due to financial constraints we did not have a baseline cTnT or ECHO available for patient reference. Also the cTnT sample was taken only once and not serially. This could have led to under-estimation of the prevalence of myocardial injury. Not all study participants had a post-infusion ECHO available.

## 5.5 Conclusions

1. The prevalence of myocardial injury in children on cancer chemotherapy as determined by an elevated cTnT was 32%. Only 9% of the study participants had abnormal Left ventricular FS as determined by ECHO.
2. Cumulative anthracycline dose is a significant risk factor for myocardial injury, with a cumulative dose of $>175$ mg/m$^2$ being associated with a tenfold increased risk in elevated cTnT.
3. Having a diagnosis of Nephroblastoma was also associated with an increased risk of elevated cTnT.

**5.6 Recommendations**

1. Cardiac troponin T should be considered as a screening test for children on cancer chemotherapy. When compared ECHO which is the current standard of care, cTnT is cheaper, more easily available in KNH and easier to interpret.

2. Children with a diagnosis of Nephroblastoma and those who require a cumulative anthracycline dose of >175 mg/m$^2$, should be prioritised for screening with cTnT.

3. Patients who require a cumulative anthracycline dose of > 175 mg/m$^2$ should receive a safer anthracycline formulation such as pegylated liposomal Adriamycin or Dexrazoxane, both of which have been shown to reduce myocardial injury.

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# APPENDICES

## APPENDIX I: PATIENT DATA COLLECTION SHEET

Cross-sectional study to determine the prevalence of myocardial injury as determined by elevated cardiac troponin T, in children on cancer chemotherapy at Kenyatta National Hospital.

Date of assessment: _____INITIALS: _____

Study No._____          Recruitment site: _____

Age: _____          Gender: _____

Weight: _____ Height: _____          W/H z score_____

Malignancy: _____

Stage of Malignancy: stage 1 _____

      Stage 2_____

      Stage 3_____

      Stage 4_____

Treatment regimen:

1) CHOPP_____          2) VAC_____ 3) VAC-CIS_____

 4)  ICE_____          5) DAT_____ 6) OTHER_____

Date Rx started: _____          Duration of Rx: _____

Cumulative dose of Doxorubicin: _____

Cumulative dose of alkylating agent:

 1) Cyclophosphamide:_____

 2) Iphosphamide:_____

History of spinal or mediastinal Radiation: yes_____ No_____ Amount in Rads: _____

Haemoglobin (g/dl)     _____

Cardiac troponin T Level: _____ ng/ml

Sample Collection date: _____

# APPENDIX II: ECHO DATA COLLECTION SHEET

Echo For patients enrolled in the study of myocardial injury in children on cancer chemo-therapy at KNH.

INITIALS: _____STUDY NO.: _____

Date: _____

Indicate if Pre-infusion ECHO: _____ Post-infusion ECHO: _____

AO: _____          HR: _____ SV: _____

LA: _____          CO: _____ LVEDD: _____

LVESD: _____ FS: _____

LVEF: _____

Diastolic Dysfunction:   E wave=          A Wave=          E/A RATIO=

CONCLUSION: _____

Other com    cvfments:_____

NOTE: Based on the American Cardiology committee of children with cancer study, cardiac dysfunction is defined as:

Ejection Fraction < 55%

     OR

Fractional shortening < 29%

Echo done by: _____

Investigator: Dr Esther Kimani.

## APPENDIX III: CONSENT FORM

For subject participating in the study "early myocardial injury, as revealed by Cardiac troponin T, in children on cancer chemotherapy at Kenyatta National hospital".

STUDY NO.: _____

INVESTIGATOR

| NAME | DEPARTMENT | CONTACT |
|------|-----------|---------|
| Dr. Esther Kimani | Paediatrics and child health UON | 0721-499717 |

KNH/UON Ethics and research committee contact- 020 726300-9

INVESTIGATOR'S STATEMENT.

My name if Dr. E. Kimani (Investigator) of the Department of paediatrics University of Nairobi. I am conducting a study to looking at the functioning of the heart in children on treatment for cancer. I am asking your consent to volunteer for a research study. Before you decide whether to take part in the study, I would like to explain the purpose, risks and benefits of the study. I will tell you what I would expect of you if you agree to be in the study. It is important that you understand that it is your choice to participate in this study. You will not be discriminated against if you do not want to participate. This form will help you decide if you want to take part in this study. If you choose to be a part of this study, I will ask you to sign your name or make your mark on this form. This process is called informed consent. It is important that you know the following:

- You do not have to be in this study if you do not want to join.
- If you join the study, you can withdraw from the study at any time.
- If you decide not to take part in this study, you can still join another research study later.

**PURPOSE OF THE STUDY**

Cancer in children in treated using various ways, including use of medication (chemo-therapy) and radiation (radiotherapy). These methods can sometimes affect the some body organs including the heart.

By carrying out this study, I seek to establish which drugs or combination of drugs are more likely to affect the heart and at what dosages. I will be using a special blood test that will inform me whether the heart of the child has been affected. I will also look at the child's heart using echocardiography, which is an imaging test that will enable us to visualise the child's heart and establish if there is any heart problem.

**BENEFITS OF THE STUDY**

This information will in future help other clinicians to establish protocols for early detection of cardiotoxicity, followed by reduction in drug dosages that can affect the heart. Information of your child's cardiac status obtained by Cardiac troponin T and echocardiography, will be given to your primary doctor. Where cardiac disease is established, the attending cardiologist will prescribe appropriate treatment. The Cardiologist will continue to review the patient when necessary, thereafter.

**PROCEDURE**

If you volunteer your child to participate in this study, I will ask you few questions concerning your child's health and carry out a physical examination. A specialist doctor will look at the way your child's heart is working using a special machine called and Echocardiogram (ECHO). This information will be recorded and entered into a patient data sheet. After this I will draw a 2 ml blood sample form the child and send it to the laboratory. This test will tell us if the child's heart has any problem.

**RISKS, STRESS OR DISCOMFORT**

Drawing of the blood sample from the child will cause a little discomfort. ECHO is a painless, non-invasive method of assessing the function of the heart and therefore, there will be no physical pain or psychological stress during the ECHO examination.

**OTHER INFORMATION:**

Participation is voluntary. There will be no extra cost to you for the ECHO or the Blood test.

The results of the tests will be kept confidential and availed to your child's primary doctor only.

Ongoing care of your child will take first priority and at no time will participation in this study interfere with your child's primary care.

You may quit this study at any stage without any obligation or penalty and the management of your child will not be compromised.

**PARTICIPANTS STATEMENT.**

The study described above has been explained to me. I agree to volunteer my child to participate in this study. I have had a chance to ask questions, I have been told that if I have future questions about the research or about my rights as a subject, I can ask the investigator. I have been told that I am free to withdraw my child from the study at any time without medical management of my child being compromised.

_____    _____    _____

Name of parent/guardian            Signature                    Date

_____    _____    _____

Investigator                       Signature                    Date

**KIAMBATANISHO III: FOMU YA RIDHAA**

Kwa mshiriki katika utafiti "kiwango cha kuhusika cha kuumia Kwa moyo, jinsi ina-vyoonekana kutumia kipimo maalum cha moyo (TroponinT) miongoni mwa watoto wanaotibiwa na dawa za saratani, katika hospitali ya kitaifa ya Kenyatta".

NAMBARI YA USAJILI YA UTAFITI: _____

MPELELEZI

| JINA | IDARA | NAMBARI YA SIMU |
|------|-------|-----------------|
| Dr. Esther Kimani | Paediatrics and child health UON | 0721-499717 |

KNH/UON Idara ya Maambatano na Utafiti: nambari ya simu- 020 726300-9

KAULI YA MPELELEZI

Jina langu ni Dr. E. kimani (mpelelezi) kutoka idara ya watoto ya chuo kikuu cha Nairo-bi. Ninafanya utafiti wa kuangalia jinsi moyo unavyofanya kazi kwa watoto wanaotibiwa saratani. Ningependa kuomba kujitolea kwako kuwa muhusika wa utafiti. Kabla ya kuamua kama utahusika katika utafiti huu, ningependa kukueleza madhumuni, hatari and manufaa ya utafiti huu. Ni Kauli yako kuwa muhusika wa utafiti huu. Ukikuba-li,nitakuomba utie sahihi kwa formu hii. Ni muhimu ujue ya kwamba:

- Sio lazima uwe muhusika wa utafiti huu kama hutaki.
- Unaweza kujiondoa kutoka utafiti huu wakati wowote

**MADHUMUNI YA UTAFITI**

Saratani ya watoto hutibiwa kutumia njia mbalimbali, ikiwa ni pamoja na madawa (chemotherapy) na mionzi (radiotherapy). Njia hizi mara nyingine zinaweza kuathiri vi-ungo fulani vya mwili ikiwa ni pamoja na moyo.

Kupitia utafiti huu, ninatafuta kubaini ni dawa zipi, au mchanganyiko upi wa dawa ulio na uwezekano zaidi wa kuathiri moyo wa mtoto, na katika kipimo kipi cha dawa. Nita-tumia kipimo maalum cha damu kitakacho niwezesha kufahamu ikiwa moyo wa mtoto umeathirika. Pia nitautazama moyo wa mtoto kutumia chombo maalum (echocardiog-raphy) kitakacho niwezesha kubaini ikiwa kuna tatizo lolote moyoni.

**FAIDA YA UTAFITI**

Maelezo haya yatawasaidia madaktari wengine siku za usoni kuanzisha itifaki za kuwezesha kugundua mapema kuathirika kwa moyo, ili kupunguza vipimo vya dawa vinavyoathiri moyo.

Maelezo ya hali ya moyo wa mtoto wako, itakayopatikana kupitia kipimo maalum cha damu (cardiac troponinT) na utazamaji wa moyo kutumia chombo maalum (echocardiography) yatapewa daktari wako wa msingi. Ikiwa ugonjwa wa moyo utapatikana, daktari mkuu wa moyo ataagiza dawa mwafaka, na ataendelea kumfwatilia mtoto baadaye ikiwa itahitajika.

**UTARATIBU**

Ikiwa utajitolea kuhusisha mtoto wako katika utafiti huu, nitakuuliza maswali chache kuhusu afya ya mtoto wako, kisha nifanye uchunguzi wa kimwili. Baada ya hiyo, nitateka damu kiasi cha mililita mbili (2mls) na nitume kwenye maabara. Kipimo hiki kitatueleza ikiwa moyo wa mtoto una shida yoyote. Baadaye daktari mtaalamu atachunguza jinsi moyo wa mtoto wako unavyofanya kazi, akitumia chombo maalum (echocardiogram). Matokeo ya uchunguzi huu yatanakiliwa kwenye karatasi ya maelezo ya mgonjwa.

**HATARI, MATATIZO AU USUMBUFU**

Utekaji damu kutoka kwa mtoto utasababisha usumbufu mdogo. Uchunguzi wa moyo kutumia kifaa maalum (echo) hauna uchungu wala hauitaji kudungwa au kupasuliwa kwa mwili wa mtoto, kwa hivyo hakutasababisha usumbufu wa mawazo au uchungu wa kimwili.

**MAELEZO MENGINE**

Kushiriki ni kwa hiari yako. Hakutakuwa na gharama ya ziada kwa kipimo cha damu au uchunguzi wa moyo.

Matokeo ya uchunguzi yatawekwa siri na yatapewa daktari wa msingi wa mtoto wako peke yake.

Matibabu yanayoendelea ya mtoto wako yatapewa kipaumbele na hakuna wakati hata mmoja ambapo ushiriki kwenye utafiti huu utaingilia kati matibabu ya kimsingi ya mtoto wako.

Uko huru kujiondoa kutoka kwa utafiti huu bila kuwajibika wala kuadhibiwa, na matibabu ya mtoto wako hayataathirika.

**KAULI YA MSHIRIKI**

Nimefafanuliwa utafiti ulioelezwa hapo juu. Nakubali kujitolea kuhusisha mtoto wangu kushiriki kwenye utafiti huu. Nimepewa nafasi ya kuuliza maswali, nimearifiwa kuwa ikiwa nitakuwa na maswali baadaye kuhusu huu utafiti, ama kuhusu haki zangu kama mshiriki, naweza kumuuliza mpelelezi. Nimeelezwa kuwa niko huru kumuondoa mtoto wangu kutoka kwa utafiti wakati wowote bila kuathirisha matibabu ya mtoto wangu.

_____      _____            _____

Jina la mzazi/mlezi                      Sahihi ya mzazi/mlezi                     Tarehe

_____      _____            _____

Shahidi                                       Sahihi ya shahidi                           Tarehe

## APPENDIX IV: ASSENT FORM (FOR 6-18 YEAR OLDS)

For subject participating in the study "early myocardial injury, as revealed by Cardiac troponin T, in children on cancer chemotherapy at Kenyatta National hospital".

INVESTIGATOR

| NAME | DEPARTMENT | CONTACT |
|------|-----------|---------|
| Dr. Esther Kimani | Paediatrics and child health UON | 0721-499717 |

KNH/UON Ethics and research committee contact- 020 726300-9

INVESTIGATOR'S STATEMENT

1.Purpose and Benefits.

You have an illness and you have been taking medications to fight the illness. The medicine that you take while at the hospital,prevents your illness from becoming serious. Often children with this illness might have other problems that can involve even their hearts. I want to find out how many children get such problems and what contributes to it. I would also like to see whether you have any problem with your heart. You will continue to get you medication and be seen by your doctor as usual.

2. Procedures

If you agree, I will examine you to make sure that you are alright. I will then use a special machine to look at your heart. This machine will tell me how your heart is beating. I will also take some blood from your arm soon after you have received your medication. This blood will also help me to know how your heart is working.

3. Risks

The test that looks at your heart using the machine is painless. The need might hurt when we take blood from your arm.

4. Other information

I will not tell anyone that you took part in this study. You do not have to take part in this study if you do not want to.  No one will be unhappy with you. You will get a copy of this paper to keep. If you have any questions, please feel free to ask me.

**B. SUBJECT'S STATEMENT**

This research study has been explained to me. I agree to take part in this study. I have had a chance to ask questions. If I have more questions I know I can ask a doctor later.

_____  _____  _____

Participant Name    Signature/Thumbprint    Date

_____  _____  _____

Witness Name     Signature       Date

(If guardian is illiterate)

_____  _____  _____

Investigator's Name   Signature        Date

**KIAMBATANISHO IV: FOMU YA RIDHAA (Wahusika wa miaka sita hadi kumi na nane)**

Kwa mshiriki katika utafiti "kiwango cha kuhusika cha kuumia Kwa moyo, jinsi inavyoonekana kutumia kipimo maalum cha moyo (TroponinT) miongoni mwa watoto wanaotibiwa na dawa za saratani, katika hospitali ya kitaifa ya Kenyatta".

**MPELELEZI**

| JINA | IDARA | NAMBARI YA SIMU |
|------|-------|-----------------|
| Dr. Esther Kimani | Paediatrics and child health UON | 0721-499717 |

KNH/UON Idara ya Maambatano na Utafiti: nambari ya simu- 020 726300-9

KAULI YA MPELELEZI

**MADHUMUNI AND FAIDA**

Uko na ugonjwa ambao umekuwa ukipata madawa hapa hospitalini,ili kupunguza makali ya ungonjwa huu. Watoto walio na ugonjwa kama huu,wanaweza kupata shida zingine kama vile shida za roho. Ningependa kujua idadi ya watoto walio na shida hii. Pia ningependa kujua kama uko na shida yeyote ya roho. Utaendelea kupata matibabu yako na utaendelea kumwona daktari wako kama kawaida.

**UTARATIBU**

Ukikubali,nitakuangalia ile kuhakikisha hauna shida yeyote. Nitaangalia roho yako inavyopiga kwa kutumia machine maalum.Baadaye,nitachukuwa kiasi kidogo cha damu kutoka kwa mkono wako. Damu hii itanisaidia kujua hali ya roho yako.

**USUMBUFU**

Hautahisi uchungu wowote tutakapo tumia machine kuangalia roho yako. Uneweza kuhisi uchungu kidogo tunapo toa damu kutoka kwa mkono.

**MAELEZO MENGINE.**

Sitaeleza mtu yeyote ya kwamba ulihusika katika utafiti huu. Sio lazima uhisike katika utafiti huu kama hutaki. Hakuna atakaye kasirishwa nu kutukuhusika kwako. Utapata nakala ya formu hii. Kama uko na maswali yeyote una uhuru wa kuuliza.

**KAULI YA MSHIRIKI**

Nimeelezwa kwa kina kuhusu utafiti huu. Nimekubali kuhusika katika utafiti huu. Nimepata nafasi ya kuuliza maswali. Kama niko na maswali mengine,nimeelezwa ninweza kumuuliza daktari.

_____         _____      _____

Jina la Mshiriki                              Sahihi/alama ya kidole                tarehe

_____              _____      _____

Shahidi                                        Sahihi/alama ya kidole                Tarehe

_____            _____      _____

Jina la mpelelezi                                     Sahihi                             Tarehe.